REMARKS

Claims 1, 2, 3, 4, 5, 6, 8, 9, and 10 have been amended for greater clarity. The amendments are fully supported by the original specification (see, *e.g.*, the paragraph bridging pages 9 and 10; page 10, lines 6-17; page 11, lines 17-20; and working examples on pages 28-30). Claim 49 has been added. Support for new claim 49 can be found throughout the specification (*e.g.*, page 10, lines 1-2). No new matter has been introduced. The amendments are made solely to expedite prosecution of the application, and Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Election/Restriction

The Office Action has acknowledged Applicants' election of Group I (claims 1-10) and election of CCR7 and a mutated form or mimic of CCL21 in the Response filed on June 6, 2005. As a result, claims 7-8 and 10-48 are withdrawn from consideration as being allegedly directed to a non-elected invention.

In response, Applicants respectfully submit that claims 7-8 and 10 depend from claim 1 and contain all the limitations thereof. Applicants respectfully direct the Examiner's attention to MPEP 809, which states that upon allowance of a generic linking claim, "[a]ny claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or includes all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability." Reconsideration and reinstatement of claims 7-8 and 10 are respectfully requested in light of the above arguments should claim 1 be found allowable.

Oath/Declaration

The Office Action asserts that the oath or declaration is allegedly defective because non-initialed and/or non-dated alterations have been made to the oath or declaration. In response, Applicants note that although the inventors (Alexander V. Chervonsky and Alexei Y. Savinov) made alternations to their addresses, the alternations were dated and initiated or signed by each of the inventors, which meets the requirements of CRF 1.52(c). A copy of the

executed declaration is enclosed herewith as **Exhibit A**. Clarification is respectfully requested.

Claim Objections

The Office Action objects to claims 1-6 and 9 because they allegedly contain reference to "CCL21" and "CCR7" without first disclosing the meaning of the acronyms in the claims. Applicants contend that these two terms are well known in the art and a skilled artisan would readily know the meanings of these two acronyms. Nevertheless, solely to expedite prosecution, Applicants have amended claims 1 and 6 to fully express these two terms and identify the acronym in parentheses. Reconsideration and withdrawal of this objection are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5-6, and 9 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. To support this rejection, the Examiner relies on the eight factors set forth in *In re Wands*.

Specifically, although the Examiner acknowledges that the specification is enabling for inhibiting the homing of insulin-sensitive $CD8^+$ T cells by administration of pertussis toxin or an anti-CCL21 antibody, or an N-terminally truncated SLC which antagonizes SLC binding to CCR7, or the N-terminally truncated CCL21 antagonist of the prior art, the Examiner asserts that the specification does not reasonably provide enablement for modulating the homing of T cells to pancreas by administration of an agonist or antagonist of the chemokine CCL21 (see Office Action, page 3, lines 14-20).

Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

As describe above, Applicants have amended claims 1-6 and 8-10 to more particularly point out certain embodiments of the invention. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Independent claim 1 as amended is directed to a method of inhibiting islet-specific homing of $CD8^+$ T cells to the pancreas in an individual having insulin-dependent diabetes, comprising contacting the cells with an antagonist of the CC chemokine ligand 21 (CCL21), in an amount sufficient to inhibit islet-specific homing of the $CD8^+$ T cells to the pancreas in the individual, wherein the $CD8^+$ T cells are specific to an islet antigen. Also, new claim 49 has been added to specify that the $CD8^+$ T cells are specific to insulin. All pending claims relate to inhibition of islet-specific homing of $CD8^+$ T cells that are specific to an islet antigen (*e.g.*, insulin) by an antagonist of CCL21. Thus, the Examiner's enablement rejections with respect to these claims have been obviated.

Applicants further submit that the specification is broadly enabling for the methods in the amended claims. For example, the specification teaches "Applicants' discovery that signaling through chemokine (*e.g.*, CCL21) and a chemokine receptor(s) regulates the islet-specific homing of diabetogenic T cells (*e.g.*, insulin-specific $CD8^+$ T cells) and thus contributes to IDDM development." See, *e.g.*, page 10, lines 6-9. The specification also provides working examples demonstrating that the SLC chemokine plays a critical role in IS-$CD8^+$ T cells homing to the islets of Langerhans and is likely to act in concert with recognition of an islet-specific peptide (*e.g.*, insulin) presented by endothelial cells. See, *e.g.*, page 28 line 17 – page 30, line 16; and Figure 6.

In particular, the Examiner asserts that "notwithstanding an antibody to CCL21, a few N-terminal truncations of CCL21 disclosed in the prior art, neither the specification nor the prior art teach additional 'antagonists' . . ." (Office Action, page 5, lines 5-8).

Applicants respectfully disagree. The specification describes that "antagonists of CCL21 include compounds (agents) which reduce or inhibit functions of CCL21. Functions of CCL21 include, but are not limited to, CCL21 activity (*e.g.*, the ability to interact with a chemokine receptor and to elicit intracellular signaling events) and CCL21 expression level. For example, agonists or antagonists of CCL21 can be an antibody against CCL21, a mutated form or a mimic of CCL21, or a peptidomimetic" (see, *e.g.*, page 11, lines 18-23). Although the specification discloses an antibody to CCL21 as a working example, Applicants are not required to provide examples of additional CCL21 antagonists because one of skill in the art would readily apply other CCL21 antagonists in the claimed method without undue

experimentation given the ample teachings of the specification. Pursuant to MPEP 2164.02, "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount experimentation. *In re Borkowski*, 442, F.2d 904, 908, 164 USPQ 642,645 (CCPA 1970)."

In view of the teachings of the specification and the ordinary knowledge in the art, one of skill in the art can readily inhibition islet-specific homing of $CD8^+$ T cells that are specific to an islet antigen (*e.g.*, insulin) by use of an antagonist of CCL21 in an individual having insulin-dependent diabetes. Accordingly, the specification and the pending claims as amended enable one of skill in the art to practice the invention without undue experimentation. Applicants respectfully request that the Examiner withdraw all enablement rejections under 35 U.S.C. § 112, first paragraph.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner further rejects claim 4 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner asserts that "[t]he specification provides no agonist or antagonist that modulates the expression of CCL21, nor does it provides any evidence by way of examples or guidance for the making or usefulness of modulating CCL21 expression in the modulating of T-cell homing to the pancreas" (see Office Action, the paragraph bridging pages 6 and 7).

Applicants respectfully traverse this rejection. Applicants have provided arguments above that independent claim 1 as amended and claims depending therefrom enable one of skill in the art to practice the invention without undue experimentation.

Further, the specification teaches in detail that CCL21 is an important target for inhibiting $CD8^+$ T cells homing to the islets and that CCL21 expression is likely to act in concert with recognition of an islet-specific peptide presented by endothelial cells (see, *e.g.*, page 28 line 17 – page 30, line 16; and Figure 6). Thus, one of skill in the art would readily appreciate the usefulness of inhibiting CCL21 expression in the inhibition of T-cell homing to the pancreas. Since methods of making agents (*e.g.*, antisense and siRNA nucleic acids) for inhibiting a gene expression are routine and known in the art at the time this application was filed, Applicants remind the Examiner that "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art

will be able to practice it without an undue amount experimentation. *In re Borkowski*, 442, F.2d 904, 908, 164 USPQ 642,645 (CCPA 1970)." See MPEP 2164.02.

Accordingly, claim 4 enables one of skill in the art to practice the invention without undue experimentation. Applicants respectfully request that the Examiner withdraw this enablement rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-6 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that "the specification has not described, nor can it be reasonably visualized by one skilled in the art, the structural and functional elements attributable agonists, antagonists, modulators, mutants, or mimics of CCL21, which represents a potentially enormous number of undisclosed and undefined organic or inorganic compounds, polypeptides, or nucleic acids" (see Office Action, the paragraph bridging pages 7 and 8).

Applicants submit that where, as in this case, (1) the inventive portion of the subject matter is disclosed and (2) any additional variability within the genus arises due to additional elements that are not part of the inventor's contribution, and when the level of knowledge and skill in the art would allow one skilled in the art to recognize that the applicant was in possession of the genus, the written description cannot be deemed defective. See Written Description Guidelines Training Materials available at, http://www.uspto.gov/web/offices/pac/writtendesc.pdf (released March 1, 2000, Example 8, page 35).

As described above, Applicants have amended independent claim 1 and its dependent claims to recite an antagonist of CCL21 only, solely to expedite prosecution of the application.

Further, Applicants contend that the claimed subject matter is described sufficiently in the specification to indicate that Applicants were in possession of the invention at the time of filing. For example, Applicants direct the Examiner's attention to page 14, line 14 – page 16, line 28, which clearly supports the antagonist of CCL21 in the claimed method. The Written

Description Guidelines for the Examination of Patent Applications state that "whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors." The factors which should be considered include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." Written Description Guidelines for the Examination of Patent Applications, section II, page 1106, column 2 (see also MPEP 2163).

Applicants submit that the specification satisfies the above guidelines. The specification provides a detailed description of the features of CCL21 antagonists of the claimed invention. For example, the specification describes that "agonists and antagonists of either CCL21 or a chemokine receptor (e.g., CCR7 or CXCR3) include any compound (agent) which modulates functions of CCL21 or the chemokine receptor, such as a protein, peptide, small organic molecule, nucleic acid, peptidomimetic, soluble chemokine receptor, and antibody" (see, *e.g.*, page 11, lines 15-18). Further, not only does the specification provide working examples illustrating the CCL21 antagonists (*e.g.*, an antibody against CCL21), it also describes a variety of screening methods for identifying antagonists of CCL21 (see, *e.g.*, page 17, line 4 – page 19, line 17).

In addition, at the time this application was filed, other CCL21 antagonists (*e.g.*, a mutated form of CCL21) and methods of making and identifying other CCL21 antagonists (*e.g.*, antisense and siRNA nucleic acids, or a small molecule inhibitor) were known and understood. In accordance with the written description guidelines and the MPEP, "[i]nformation which is well known in the art need not be described in detail in the specification." Written Description Guidelines for the Examination of Patent Applications, section II, page 1105, column 3; MPEP 2163.

For the above reasons, Applicants maintain that all pending claims are supported by the specification with sufficient detail, and in light of the detailed description provided in the specification and the high level of skill in the art, that Applicants were in possession of the claimed invention at the time this application was filed. Accordingly, reconsideration and withdrawal of rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 102(a)

Claims 1-3, 5-6, and 9 are rejected under 35 U.S.C. § 102(a) as being allegedly anticipated by Sasaki *et al.* (January 1, 2003). Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

Sasaki *et al.* fail to teach or suggest each and every limitation of the present claims. In accordance with MPEP 2131 and with the Courts, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros.v. Union Oil Co, of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

As described above, independent claim 1 as amended is directed to a method of inhibiting islet-specific homing of $CD8^+$ T cells to the pancreas in an individual having insulin-dependent diabetes, comprising contacting the cells with an antagonist of the CC chemokine ligand 21 (CCL21), in an amount sufficient to inhibit islet-specific homing of the $CD8^+$ T cells to the pancreas in the individual, wherein the $CD8^+$ T cells are specific to an islet antigen.

By contrast, Sasaki *et al.* merely disclose evaluation of the preventive effect of certain CCL21 antagonists (i.e., truncated forms of CCL21) on chronic graft-vs-host disease (GVHD) in a murine model by blocking the homing of donor CCR7-expressing T cells into the recipient's lymphoid organs. However, Sasaki *et al.* neither teaches nor suggests inhibition of islet-specific homing of $CD8^+$ T cells to the pancreas in an individual having insulin-dependent diabetes, comprising contacting the cells with an antagonist of the CC chemokine ligand 21 (CCL21), in an amount sufficient to inhibit islet-specific homing of the $CD8^+$ T cells to the pancreas in the individual, wherein the $CD8^+$ T cells are specific to an islet antigen, as recited in the claimed invention. Accordingly, Sasaki *et al.* neither teach nor suggest all the elements of the claimed invention and fail to anticipate the method of claim 1. For the same reasons, all claims depending from claim 1 are novel over Sasaki *et al.* Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 102(a).

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-3 are rejected under 35 U.S.C. § 102(b) over Hermida *et al.* (1991). Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

Hermida *et al.* merely disclose that treatment of rats with pertussis toxin resulted in a reversal of the usual plasma glucose and insulin response elicited by intravenously administered lithium. However, Hermida *et al.* neither teaches nor suggests inhibition of islet-specific homing of $CD8^+$ T cells to the pancreas in an individual having insulin-dependent diabetes, comprising contacting the cells with an antagonist of the CC chemokine ligand 21 (CCL21), in an amount sufficient to inhibit islet-specific homing of the $CD8^+$ T cells to the pancreas in the individual, wherein the $CD8^+$ T cells are specific to an islet antigen, as recited in the claimed invention. Accordingly, Hermida *et al.* neither teach nor suggest all the elements of the claimed invention and fail to anticipate the method of claim 1. For the same reasons, all claims depending from claim 1 are novel over Hermida *et al.* Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 102(b).

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-3 and 5-6 are rejected under 35 U.S.C. § 102(b) over Engeman *et al.* (2000). Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

Engeman *et al.* merely disclose that administration of an anti-CCL21 antibody to a mouse model of T cell-mediated inflammation (contact hypersensitivity) resulted in inhibition of Langerhans cell migration into draining lymph nodes. However, Engeman *et al.* neither teaches nor suggests inhibition of islet-specific homing of $CD8^+$ T cells to the pancreas in an individual having insulin-dependent diabetes, comprising contacting the cells with an antagonist of the CC chemokine ligand 21 (CCL21), in an amount sufficient to inhibit islet-specific homing of the $CD8^+$ T cells to the pancreas in the individual, wherein the $CD8^+$ T cells are specific to an islet antigen, as recited in the claimed invention. Accordingly, Engeman *et al.* neither teach nor suggest all the elements of the claimed invention and fail to

anticipate the method of claim 1. For the same reasons, all claims depending from claim 1 are novel over Engeman *et al.* Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 102(b).

CONCLUSION

In view of the above remarks, Applicants believe that the pending application is in condition for allowance. Early and favorable reconsideration is respectfully solicited. Applicants believe that no further fee is due with this response. However, if a fee is due, please charge our **Deposit Account No. 18-1945**, under Order No. **JMY-P01-001** from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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